Please add the following claims:

5. (New) The composition according to claim 1, wherein the PQQ-dependent glucose dehydrogenase content is 5 to 50 % by weight.

6. (New) The composition according to claim 1, wherein the PQQ-dependent glucose dehydrogenase is derived from genera Acinetobacter.

7. (New) The composition according to claim 1, wherein the PQQ-dependent glucose dehydrogenase is derived from Acinebacter calcoaceticus.

8. (New) The composition according to claim 1, wherein the PQQ-dependent glucose dehydrogenase is derived from Acinebacter calcoaceticus NCIMB11517.

9. (New) The method according to claim 3, wherein the PQQ-dependent glucose dehydrogenase content is 5 to 50 % by weight.

10. (New) The method according to claim 3, wherein the PQQ-dependent glucose dehydrogenase is derived from genera Acinetobacter.

11. (New) The method according to claim 3, wherein the PQQ-dependent glucose dehydrogenase is derived from Acinebacter calcoaceticus.

12. (New) The method according to claim 3, wherein the PQQ-dependent glucose dehydrogenase is derived from Acinebacter calcoaceticus NCIMB11517.

REMARKS

The Present Invention and Pending Claims

Claims 1-2 and 5-8 are directed to a stable composition comprising a PQQ-dependent glucose dehydrogenase, and claims 3-4 and 9-12 are directed to a method of preparing the composition. The composition of the present invention has a much higher specific activity relative to the total weight of the composition than other such compositions known in the art. Additionally, the amount of stabilizing agent contained in the composition of the present invention is remarkably low. These characteristics have several advantages, including the reduction of a potential adverse effect on an enzyme reaction by impurities which may be

contained in the stabilizing agent, and the reduction of errors in measuring small amounts of solution with pipettes and the like, as a result of the low viscosity of solution due to the low concentration of a stabilizing agent. Moreover, since the enzyme composition of the present invention is primarily intended to be utilized as a sensor of blood glucose, whereby the enzyme composition is applied to a sensor tip, the high specific activity of the composition means that only a small amount of the composition is needed for application, which assists in the reduction of scatter in the measured values.

The Amendments to the Claims

Claim 3 has been amended to point out more particularly and claim more distinctly the present invention. Claims 5-12 are new, and are supported by the specification at, for example, page 5, lines 13-19; page 5, line 24, through page 6, line 1; and page 10, lines 3-6. No new matter has been added by way of these amendments. Separate documents setting forth the amendments to the claims, as well as the text of all of the pending claims as amended, are enclosed.

The Office Action

The Office has rejected claims 3 and 4 under 35 U.S.C. § 112, first paragraph, as allegedly incorporating new matter. In addition, claims 1-4 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite. The Office has rejected claims 1-4 under 35 U.S.C. § 103(a) as obvious over Sode et al. (*Biotechnology Techniques, 11*(8), 577-580 (1997)) in view of Adachi et al. (JP 09-140378). Reconsideration of these rejections is hereby requested.

Discussion of Rejection under 35 U.S.C. § 112, first paragraph

The Office contends that there is no support in the specification for adding the enzyme in an amount of 100 to 2000 kU per gram of the total components calculated on a dry basis as recited in claims 3 and 4. These claims, as amended, recite a method for making a composition having a glucose dehydrogenase (GDH) content of 100 to 2000 kU per gram of the composition.

The specification supports this characteristic of the claims at, for example, page 5, line 24, through page 6, line 3. Specifically, at page 6, lines 2-3, the specification recites that the "GDH content calculated as enzyme activity is preferably 100 to 2000 U/mg." Units per milligram is equivalent to kiloUnits per gram.

Additionally, as shown in the accompanying Rule 132 Declaration of Seiji Takeshima, Compositions 4-9 of Table 1 of Example 1 (page 9) and Compositions 2-3 of Table 2 of Example 2 (page 10) have glucose dehydrogenase contents (calculated as enzyme

activity) of between 868 and 950 kU/g, which is within the range of 100-2000 kU/g recited in claims 1 and 3.

For the foregoing reasons, the rejection of claims 3 and 4 under Section 112, first paragraph, should be withdrawn.

Discussion of Rejection under 35 U.S.C. § 112, second paragraph

The Office contends that claims 1-4 are indefinite because it would not be clear to an ordinary artisan what the phrase "100 to 2000 kU" [of the enzyme] per gram of the composition" means for any particular enzyme or how to easily determine the quantity of the enzyme to achieve the recited amount of 100 to 2000 kU. The specification, however, discloses that, although the glucose dehydrogenase content of the lyophilized composition is varied depending on the origin of the enzyme, a glucose dehydrogenase content of about 5 to 50% by weight is preferred (see, e.g., page 5, line 24, through page 3, line 1). Thus, one of ordinary skill in the art would have understood from reading the specification that the PQQ-dependent glucose dehydrogenase composition having a specific activity of 100 to 2000 kU/g can be prepared, for example, when the glucose dehydrogenase content of the lyophilized composition is about 5 to 50% by weight. In addition, the accompanying Rule 132 Declaration by Seiji Takeshima further supports that a PQQ-dependent glucose dehydrogenase composition having a specific activity of 100 to 2000 kU/g can be obtained using the compositions described in Examples 1 and 2.

Although claims 1-4 are believed to be definite, Applicants have added dependent claims 5-12, which recite additional characteristics of the PQQ-dependent glucose dehydrogenase composition. Claims 5-12 are even more definite as regards what the phrase "100 to 2000 kU per gram of the composition" means in relation to the present invention and how to determine the quantity of the enzyme to achieve the recited amount of 100 to 2000 kU.

Additionally, the Office alleges that claims 1-4 are indefinite because it is not clear whether the amount of enzyme is calculated on a wet or dry weight basis of the composition. The composition according to claims 1 and 2 is lyophilized. Lyophilization refers to a freeze-drying process in which water is removed from a composition by sublimation. Therefore, it is clear that the weight recited in these claims refers to dry weight. In claims 3 and 4, the weight of the total components refers to the weight of the constituents, which would be regarded as a dry weight. Thus, one of ordinary skill in the art, upon reading claims 1-4, would understand that the amount of enzyme is calculated on a dry weight basis of the composition.

For the above reasons, claims 1-4 are definite, and the rejection under Section 112, second paragraph, should be withdrawn.

Discussion of Rejection under 35 U.S.C. § 103(a)

The obviousness rejection of claims 1-4 over the Adachi and Sode references has been maintained by the Office. In the previous Response to Office Action dated July 30, 2002, Applicants argued the Adachi reference does not teach or suggest a composition or method involving the use of the composition, wherein the composition comprises a PQQ-dependent glucose dehydrogenase with an enzyme activity that is 100 to 2000 kU per gram of the total components. In fact, the Adachi reference does not specify any specific activity of the PQQ-dependent glucose dehydrogenase. The Applicants, however, determined from Example 4 of the Adachi reference that the glucose dehydrogenase activity relative to the total dry weight in the aqueous composition is about 0.18 kU/g. The composition of the pending claims has an enzyme activity of 100 to 2000 kU glucose dehydrogenase/g, which is remarkably higher than that of the Adachi reference (at least 556 times higher). Thus, the Adachi reference does not teach or suggest an enzyme activity within the range recited in the pending claims.

Applicants further argued that the Sode reference does not cure the deficiencies of the Adachi reference in the manner necessary to arrive at the present invention. The enzyme composition taught by the Sode reference does not have a PQQ-dependent glucose dehydrogenase activity of 100 to 2000 kU per gram of the total components, nor does the composition contain the stabilizing compounds recited in the pending claims. Accordingly, Applicants argued that the Sode and Adachi references did not render the pending claims obvious.

In response, the Office contends that there is no clear indication of the enzyme activity of the PQQ glucose dehydrogenase from *Acinetobacter calcoaceticus NCIMB11517.* The Office alleges that Tables 1 and 2 are directed to residual activity, not the initial activity, and therefore do not support Applicants' arguments directed to the high activity of the enzyme of the present invention compared to that disclosed by the Adachi reference. The specification, however, as described above, discloses that the glucose dehydrogenase content, as measured in terms of enzyme activity, is 100-2000 U/mg (kU/g) (see, e.g., page 6, lines 2-3). The enzyme activities of the compositions of Examples 1 and 2 are described in the Rule 132 Declaration of Seiji Takeshima as ranging from about 868 to 950 kU/g, which is within the specified parameters of 100-2000 kU/g recited in the pending claims. Thus, the enzyme activities pertaining to the present invention are much greater than the activity of 0.18 kU/g pertaining to the disclosure of the Adachi reference.

The Office contends that Applicants' showing of unexpected results is not commensurate in scope with the pending claims. Rather, the Office contends that Applicants' showing of unexpected results would only pertain to claims limited to a PQQ-dependent glucose dehydrogenase from *Acinetobacter calcoaceticus NCIMB11517*. The compositions according to claims 1 and 2, as well as the methods according to claims 3 and 4, would exhibit similar effects independent of the origins of the PQQ-dependent glucose dehydrogenase. This is because the amino acid sequences of glucose dehydrogenases derived from different origins have a high degree of homology. This homology of amino acid sequences leads to the similarity of higher structures of enzyme proteins, resulting in the similar enzymatic activities. For this reason, the unexpected results pertain to more than just PQQ-dependent glucose dehydrogenases derived from *Acinetobacter calcoaceticu NCIMB11517*. In any event, Applicants have added dependent claims 5-12, which recite additional characteristics of the PQQ-dependent glucose dehydrogenase of the present invention and which serve to further distinguish the present invention from the prior art.

As discussed in the previous Response to Office Action, the Adachi and Sode references do not teach or suggest an enzyme with the PQQ-dependent glucose dehydrogenase activity of 100 to 2000 kU per gram as required by the pending claims. Accordingly, the Adachi and Sodi references would not have led one of ordinary skill in the art to the PQQ-dependent glucose dehydrogenase composition and method of producing the composition as recited in the pending claims. Therefore, the obviousness rejection of claims 1-4 should be withdrawn.

Conclusion

The application is considered in good and proper from for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

In re Appln. of Hattori et al.
Application No. 09/781,703

Respectfully submitted,

John Kilyk, Jr., Reg. No. 30,763
LEYDIG, VOIT & MAYER, LTD.
Two Prudential Plaza, Suite 4900
180 North Stetson
Chicago, Illinois 60601-6780
(312) 616-5600 (telephone)
(312) 616-5700 (facsimile)

Date: December 20, 2002

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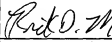
I hereby certify that this RESPONSE TO OFFICE ACTION and all accompanying documents are being deposited with the United States Postal Service "Express Mail Post Office To Addressee" Service under 37 CFR 1.10 on the date indicated below and is addressed to: Commissioner for Patents, Washington, D.C. 20231.

Rick D. Madsen		December 20, 2002
Name of Person Signing	Signature	Date